DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

962156

JAN 19 2007

WARNING LETTER

VIA FEDERAL EXPRESS

Kurt A. Dasse, Ph.D.
President
Levitronix LLC
45 First Avenue
Waltham, Massachusetts 02451

Dear Dr. Kurt A. Dasse:

During an inspection of your firm located in Zurich, Switzerland, on September 26-29, 2006, an investigator from the United States Food and Drug Administration (FDA) determined that your firm manufactures the Levitronix CentriMag® Extracorporeal Blood Pumping System and the Levitronix CentriMag® Back-Up Console. Under section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 321(h), these products are devices because they are intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or are intended to affect the structure or function of the body.

This inspection revealed that these devices are adulterated within the meaning of section 501(h) of the Act (21 U.S.C. § 351(h)), in that the methods used in, or the facilities or controls used for, their manufacture, packing, storage, or installation are not in conformity with the Current Good Manufacturing Practice (CGMP) requirements of the Quality System (QS) regulation found at Title 21, Code of Federal Regulations (C.F.R.), Part 820. These violations include, but are not limited to, the following:

1. Failure to establish and maintain adequate procedures for implementing corrective and preventive action, as required by 21 CFR 820.100(a).

   For example, the "Standard Operating Procedure, Corrective & Preventive Action" ([redacted]) does not include requirements for:

   (a) Analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems.

(b) Appropriate statistical methodology to be employed to detect recurring quality problems.

(c) When verification can be done in lieu of validation.

2. Failure to establish and maintain adequate procedures that ensure the identification of all actions needed to correct and prevent recurrence of nonconforming product and other quality problems, as required by 21 CFR 820.100(a)(3). For example:

(a) CAPAR No. [redacted] was created as a result of sixteen (16) blood pumps failing the [redacted] pump test at the contract manufacturer. The root cause was identified as "Poor quality – magnets were purchased from a new Chinese distributor." However, these magnets undergo receiving acceptance activities at the firm prior to shipping to the contract manufacturer. As such, the investigation of the cause of this nonconformity was not completely conducted. The CAPA does not identify any actions regarding the acceptance of nonconforming magnets at the firm.

(b) CAPAR No. [redacted] (Corrective and Preventive Action Request, date [redacted], under "Description of Condition/Problem") states "Levitronix has been aware of this 'cold start' behavior due to a handful of complaints from the field." However, these complaints were not referenced in this CAPA, and it is not documented that these complaints were analyzed to ensure that all necessary actions were taken to correct and prevent this nonconformance.

3. Failure to establish and maintain adequate procedures for receiving, reviewing, and evaluating complaints to ensure that all complaints are processed in a uniform and timely manner, as required by 21 CFR 820.198(a)(1).

For example, the "General Procedure, Complaint Management" ([redacted]) defines for Class B complaints "Investigation report completion three (3) months from the date of investigation assignment." However, investigation reports were not completed within the defined three-month time frame for the following complaints, and no written request for additional time was approved by RA as required by [redacted] nor made part of the file.

Complaint #	Date Assigned	Date Completed	Months Overdue
[redacted]	[redacted]	[redacted]	> 8
[redacted]	[redacted]	[redacted]	> 11
[redacted]	[redacted]	[redacted]	> 8
[redacted]	[redacted]	[redacted]	> 5
[redacted]	[redacted]	[redacted]	> 4

4. Failure to establish and maintain adequate procedures for complaint handling to ensure documentation of any corrective action taken, as required by 21 CFR 820.198(e)(7).

For example, the "General Procedure, Complaint Management" ([redacted]) states "If corrective action is warranted …, it will be completed in accordance with [redacted] 'Corrective Action & Preventive Action'." However, this was not implemented for the following complaints:

(a) Complaint #[redacted] was assigned on [redacted], due to white particles found in and around the inlet connectors of the CentriMag blood pumps. The corrective action identified for this complaint was to change the packaging of the CentriMag blood pump (Document Change Order [DCO] #[redacted]). However, a CAPAR was not created for this corrective action, and therefore there was inadequate documentation of the corrective action taken or the timeliness between the complaint and the DCO dated almost a full year later.

(b) Complaint #[redacted] was assigned on [redacted], due to the activation of the "pump not inserted" alarm after the motor was plugged into the primary console. The corrective action identified for this complaint was a software update (DCO #[redacted]). However, a CAPAR was not created for this corrective action as required in [redacted]

5. Failure to establish and maintain adequate procedures for purchasing controls to include quality requirements that must be met by suppliers, contractors, and consultants, as required by 21 CFR 820.50(a).

   For example, the "Standard Operating Procedure, Purchasing Controls" ([redacted]):

   (a) Does not define the evaluation and selection of potential suppliers, contractors, and consultants on the basis of their ability to meet specified requirements, including quality requirements.

   (b) Does not define the type and extent of control to be exercised over the product, services, suppliers, contractors, and consultants, based on the evaluation results.

6. Failure to establish and maintain adequate procedures for the identification, documentation, validation or where appropriate verification, review, and approval of design changes before their implementation, as required by 21 CFR 820.30(i). For example:

   (a) The "Standard Operating Procedure, Design Control" ([redacted] does not address when verification of pre-production design changes is sufficient in lieu of validation prior to their implementation. Also, subsection [redacted] of the procedure states "Although changes to some documents (e.g., early drawings and testing results) do not require approvals …" As such, your firm did not have adequate documentation of the review and approval of pre-production design changes.

   (b) The "Standard Operating Procedure, Design Control" ([redacted] defines the procedures for post-production design changes by referencing [redacted] "Document Control." The "Standard Operating Procedure, Document Control" ([redacted] and the "General Procedure, Document Change Order (DCO) System" ([redacted], do not define when verification of post-production design changes is sufficient in lieu of validation prior to their implementation.

7. Failure to establish and maintain adequate procedures for design verification to include acceptance criteria prior to the performance of verification activities and to ensure such acceptance criteria are met, as required by 21 CFR 820.30(f). For example:

   (a) The design verification activity conducted for "Test Case [redacted] – Audio Transducer ([redacted])" (CentriMag® Back-Up Console – Requirements Verification Test Plan, [redacted],

[redacted] does not confirm that the design output meets the design input requirements. For example, the "Expected Outputs" identified state "Verify … that the audio sound pressure level is [redacted] and that the output frequency is between [redacted]." However, the "Test Results Data Sheet – CentriMag Back-Up Console" ([redacted]) states under Output No. 2 "Audi level [redacted] at ambient noise level of [redacted] distance 1 meter" and a Pass/Fail Status of "Pass." A nonconformance and/or justification was not generated/provided for identifying a result not meeting pre-defined acceptance criteria as "Pass."

(b) Acceptance criteria were not established for "Test Case [redacted] – Simulated User Evaluation (SUE) ([redacted])" (CentriMag® Back-Up Console – Requirements Verification Test Plan, [redacted]

8. Failure to establish and maintain adequate procedures for design review to ensure that participants at each design review include representatives of all functions concerned with the design stage being reviewed and an individual who does not have direct responsibility for the design stage being reviewed, as required by 21 CFR 820.30(e).

For example, subsections [redacted] and [redacted] of the "Standard Operating Procedure, Design Control" ([redacted]) define Design Review III and IV, respectively. These subsections do not ensure that participants at each design review include representatives of all functions concerned with the design state being reviewed and an individual(s) who does not have direct responsibility for the design stage being reviewed.

9. Failure to establish and maintain adequate procedures for design input to ensure that the design requirements relating to a device are appropriate and address its intended use, as required by 21 CFR 820.30(c). For example:

(a) The "Standard Operating Procedure, Design Control" ([redacted]) states "an initial Design Input document must be created, discussed among Project Team members, and approved." However, the firm was unable to provide a copy of the initial Design Input and approval of the initial design input document.

(b) The "Standard Operating Procedure, Design Control" ([redacted]) does not include a mechanism for addressing incomplete, ambiguous, or conflicting requirements.

10. Failure to establish and maintain an adequate design and development plan which defined activities and responsibilities, as required by 21 CFR 820.30(b).

For example, the "Standard Operating Procedure, Design Control" [redacted] states that the design plan, which is defined in subsection [redacted] will be approved during Design Review I. However, your firm did not establish and maintain plans that describe or reference the design and development activities and define responsibility for implementation for the design project, CentriMag® Back-Up Console (K051209).

11. Failure to establish and maintain adequate procedures for ensuring that equipment is routinely calibrated, as required by 21 CFR 820.72(a).

For example, the calibration frequency for Equipment No. [redacted] Lot Approval Test System for DCP [redacted] which is used as an inspection and test equipment for the final acceptance activity Blood Pump Lot Proof Test, is defined as "1-Year." However, the due date following a calibration date of [redacted] was listed as [redacted], which exceeded the yearly calibration frequency by a year.

12. Failure to establish and maintain adequate procedures to ensure that the device history records (DHRs) include or refer to the location of the primary identification label and labeling for each production unit, as required by 21 CFR 820.184(e).

For example, DHRs do not include the primary identification label and labeling used for each production unit.

13. Failure to establish and maintain adequate procedures for management review, as required by 21 CFR 820.20(c).

For example, the "Standard Operating Procedure, Management Review" [redacted] does not define that the dates of quality system reviews be documented.

14. Failure to establish and maintain adequate procedures to validate with a high degree of assurance a process that cannot be fully verified, as required by 21 CFR 820.75(a).

For example, the "Report for the Second Revalidation of an Ethylene Oxide Sterilization Cycle" ([redacted] states "The next review of the Sterilization Validation is due by [redacted] ultimately or any earlier as needed ..." However, your firm's Vice President of Regulatory Affairs/Quality Assurance/Operations reported that this review was not conducted since [redacted] on which the second revalidation report was issued.

15. Failure to establish and maintain adequate procedures to prevent contamination of equipment or product by certain substances, as required by 21 CFR 820.70(e).

For example, the "General Procedure/Facility Cleaning, Maintenance/& Pest Control" ([redacted]) states "Exterminating service shall be performed monthly…" However, your firm's Production Manager reported that exterminating service was not performed.

You should take prompt action to correct the violations addressed in this letter. Failure to promptly correct these violations may result in regulatory action, which may include detaining your devices without physical examination upon entry into the United States until the corrections are completed under section 801(a) of the Act (21 U.S.C. § 381(a)). Also, U.S. federal agencies are advised of the issuance of all Warning Letters about devices so that they may take this information into account when considering the award of contracts. Additionally, premarket approval applications for Class III devices to which the Quality System regulation deviations are reasonably related will not be approved until the violations have been corrected. Requests for Certificates to Foreign Governments will not be granted until the violations related to the subject devices have been corrected.

Please notify this office in writing within fifteen (15) working days from the date you receive this letter of the specific steps you have taken to correct the noted violations, including an explanation of how you plan to prevent these violation(s), or similar violation(s), from occurring again. Include documentation of the corrective action you have taken. If your planned corrections will occur over time, please include a timetable for implementation of those corrections. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed. If the documentation is not in English, please provide a translation to facilitate our review.

Your response should be sent to: Ms. Nicole L. Wolanski, Chief of Cardiovascular and Neurological Devices Branch, HFZ-341, Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Enforcement B, 9200 Corporate Boulevard, Rockville, Maryland 20850. If you have any questions about the content of this letter, please contact: Ms. Nicole L. Wolanski at telephone (240) 276-0295 or telefax (240) 276-0129.

Finally, you should know that this letter is not intended to be an all-inclusive list of the violations at your facility. It is your responsibility to ensure compliance with applicable laws and regulations administered by FDA. The specific violation(s) noted in this letter and in the Inspectional Observations, Form FDA 483 (FDA 483), issued at the closeout of the inspection may be symptomatic of serious problems in your firm's manufacturing and quality assurance systems. You should investigate and determine the causes of the violations, and take prompt actions to correct the violation(s) and to bring your products into compliance.

Sincerely yours,

Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and
Radiological Health

cc: [redacted]
Chief Executive Officer
Levitronix GmbH
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Waltham, Massachusetts 02451